

CLAIMS

- 1 An immunostimulatory nucleic acid molecule having at least one internal pyrimidine-purine (YZ) dinucleotide and a chimeric backbone, wherein the at least one internal YZ dinucleotide has a phosphodiester or phosphodiester-like internucleotide linkage, wherein optionally each additional internal YZ dinucleotide has a phosphodiester, phosphodiester-like, or stabilized internucleotide linkage, and wherein all other internucleotide linkages are stabilized.
- 5 2. The oligonucleotide of claim 1, wherein the immunostimulatory nucleic acid comprises a plurality of internal YG dinucleotides having a phosphodiester or phosphodiester-like internucleotide linkage.
- 10 3. The oligonucleotide of claim 2, wherein every internal YG dinucleotide has a phosphodiester or phosphodiester-like internucleotide linkage.
- 15 4. The oligonucleotide of claim 1, wherein the immunostimulatory nucleic acid molecule is any one of SEQ ID NO:1 – 54, SEQ ID NO:55-99 and SEQ ID NO:241, wherein * shown in the SEQ ID No's in the specification represents phosphorothioate, _ represents phosphodiester, U represents 2'-deoxyuracil, and 7 represents 7-deazaguanine.
5. The oligonucleotide of claim 1, wherein the immunostimulatory nucleic acid molecule is selected from the group consisting of:
T*C_G*T*C_G*T*T*T*T_G*T*C_G*T*T*T*T_G*T*C_G*T*T (SEQ ID NO:100),
20 T*C_G*T*C_G*T*T*T*T_G*T*C_G*T*T (SEQ ID NO:101),
T*C_G*T*C_G*T*T*T*T_G*T*C_G*T*T (SEQ ID NO:102),
T*T_G*T*C_G*T*T*T*T_G*T*C_G*T*T_G*T*T_G*T*C_G*T*T (SEQ ID NO:103), and T*C_G*T*T_C_G*T*T*T*T_C_G*T*T_C_G*T*T_C_G*T*T (SEQ ID NO:104), wherein * represents phosphorothioate and _ represents phosphodiester.
- 25 6. A oligonucleotide, comprising: an immunostimulatory nucleic acid molecule comprising a chimeric backbone and at least one sequence N₁YGN₂, wherein independently for each sequence N₁YGN₂ YG is an internal pyrimidine-guanosine (YG) dinucleotide, N₁ and N₂ are each, independent of the other, any nucleotide, and wherein for the at least one sequence N₁YGN₂ and optionally for each additional sequence
30 N₁YGN₂:
the YG dinucleotide has a phosphodiester or phosphodiester-like internucleotide linkage, and

- (a) N₁ and Y are linked by a phosphodiester or phosphodiester-like internucleotide linkage when N₁ is an internal nucleotide,
- (b) G and N₂ are linked by a phosphodiester or phosphodiester-like internucleotide linkage when N₂ is an internal nucleotide, or
- 5 (c) N₁ and Y are linked by a phosphodiester or phosphodiester-like internucleotide linkage when N₁ is an internal nucleotide and G and N₂ are linked by a phosphodiester or phosphodiester-like internucleotide linkage when N₂ is an internal nucleotide, wherein all other internucleotide linkages are stabilized.
7. The oligonucleotide of claim 6, wherein the immunostimulatory nucleic acid comprises a plurality of the sequence N₁YGN₂, wherein for each sequence N₁YGN₂:
- 10 the YG dinucleotide has a phosphodiester or phosphodiester-like internucleotide linkage, and
- (a) N₁ and Y are linked by a phosphodiester or phosphodiester-like internucleotide linkage when N₁ is an internal nucleotide,
- 15 (b) G and N₂ are linked by a phosphodiester or phosphodiester-like internucleotide linkage when N₂ is an internal nucleotide, or
- (c) N₁ and Y are linked by a phosphodiester or phosphodiester-like internucleotide linkage when N₁ is an internal nucleotide and G and N₂ are linked by a phosphodiester or phosphodiester-like internucleotide linkage when N₂ is an internal nucleotide.
- 20
8. The oligonucleotide of claim 6, wherein the immunostimulatory nucleic acid molecule is any one of SEQ ID NO:105 – 231, wherein * shown in the SEQ ID No's in the specification represents phosphorothioate and _ represents phosphodiester.
9. The oligonucleotide of claim 6, wherein the immunostimulatory nucleic acid molecule is selected from the group consisting of:
- 25 T*C_G_T*C_G_T*T*T*T*G*T*C_G_T*T*T*T*T*G*T*C_G_T*T (SEQ ID NO:232),
- T*C_G*T_C_G*T*T*T*T*G*T_C_G*T*T*T*T*T*G*T_C_G*T*T (SEQ ID NO:233), and
- 30 T*C_G_T_C_G_T*T*T*T*T*G*T_C_G_T*T*T*T*T*G*T_C_G_T*T (SEQ ID NO:234), wherein * represents phosphorothioate and _ represents phosphodiester.

10. The oligonucleotide of claim 6, wherein the immunostimulatory nucleic acid molecule is selected from the group consisting of:

T*C*G*T*C*G*T*T*T_G*T*C*G*T*T*T_G*T*C*G*T*T (SEQ ID NO:235),

5 T*C*G*T*C*G*T*T*T_G_T*C*G*T*T*T_G*T*C*G*T*T (SEQ ID NO:236), and

T*C*G*T*C*G*T*T*T_G_T*C*G*T*T*T_G*T*C*G*T*T (SEQ ID NO:237), wherein * represents phosphorothioate and _ represents phosphodiester.

11. The oligonucleotide of claim 6, wherein the immunostimulatory nucleic acid molecule is selected from the group consisting of:

10 T*C_G*T_C_G*T*T*T_G*T_C_G*T*T*T_G*T_C_G*T*T (SEQ ID NO:238),

T*C_G_T*C_G_T*T*T*T_G_T*C_G_T*T*T*T_G_T*C_G_T*T (SEQ ID NO:239), and

15 T*C_G_T_C_G_T*T*T*T_G_T_C_G_T*T*T*T_G_T_C_G_T*T (SEQ ID NO:240), wherein * represents phosphorothioate and _ represents phosphodiester.

12. The oligonucleotide of claim 1, wherein the at least one internal YG dinucleotide having a phosphodiester or phosphodiester-like internucleotide linkage is CG.

20 13. The oligonucleotide of claim 1, wherein the at least one internal YG dinucleotide having a phosphodiester or phosphodiester-like internucleotide linkage is TG.

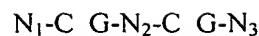
14. The oligonucleotide of claim 1, wherein the immunostimulatory nucleic acid molecule is a B-Class immunostimulatory nucleic acid molecule.

25 15. The oligonucleotide of claim 1, wherein the immunostimulatory nucleic acid molecule is a C-Class immunostimulatory nucleic acid molecule.

16. The oligonucleotide of claim 1, wherein the immunostimulatory nucleic acid molecule is 4-100 nucleotides long.

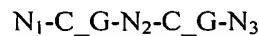
30 17. The oligonucleotide of claim 1, wherein the immunostimulatory nucleic acid molecule is not an antisense oligonucleotide, triple-helix-forming oligonucleotide, or ribozyme.

18. An oligonucleotide which comprises



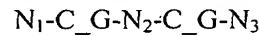
wherein N_1 and N_3 are each independently a nucleic acid sequence 1-20
nucleotides in length, wherein $\underline{}$ indicates an internal phosphodiester or phosphodiester-like internucleotide linkage, wherein N_2 is independently a nucleic acid sequence 0-20
5 nucleotides in length, and wherein $G-N_2-C$ includes 1 or 2 stabilized linkages.

19. An oligonucleotide which comprises



wherein N_1 and N_3 are each independently a nucleic acid sequence 1-20
10 nucleotides in length, wherein $\underline{}$ indicates an internal phosphodiester or phosphodiester-like internucleotide linkage, wherein N_2 is independently a nucleic acid sequence 4-20
nucleotides in length, and wherein $G-N_2-C$ includes at least 5 stabilized linkages.

20. An oligonucleotide which comprises



wherein N_1 , N_2 , and N_3 are each independently a nucleic acid sequence of 0-20
nucleotides in length and wherein $\underline{}$ indicates an internal phosphodiester or
phosphodiester-like internucleotide linkage, wherein the oligonucleotide is not an
antisense oligonucleotide, triple-helix-forming oligonucleotide, or ribozyme.
20

21. An oligonucleotide which comprises



wherein N_1 and N_2 are each independently a nucleic acid sequence of 0-20
nucleotides in length, wherein $n=2$ or $n=4-6$, wherein X_1 and X_2 are each independently a
25 nucleic acid sequence having phosphorothioate internucleotide linkages of 3-10
nucleotides, wherein $N_1-(GTCGTT)_n-N_2$ includes at least one phosphodiester
internucleotide linkage, and wherein 3' and 5' nucleotides of the oligonucleotide do not
include a poly-G, poly-A, poly-T, or poly-C sequence.

22. The oligonucleotide of claim 1 wherein the nucleic acid has a backbone
30 comprising deoxyribose or ribose.

23. The oligonucleotide of claim 1, wherein the oligonucleotide further
comprises an adjuvant or a cytokine, or an antigen.

24. The oligonucleotide of claim 1 wherein the phosphodiester or phosphodiester-like internucleotide linkage is phosphodiester.

25. The oligonucleotide of claim 1 wherein the phosphodiester-like linkage is boranophosphonate or diastereomerically pure Rp phosphorothioate.

5 26. The oligonucleotide of claim 1 wherein the stabilized internucleotide linkages are selected from the group consisting of: phosphorothioate, phosphorodithioate, methylphosphonate, methylphosphorothioate, and any combination thereof.

10 27. The oligonucleotide of claim 1 wherein the stabilized internucleotide linkages are phosphorothioate.

28. An oligonucleotide comprising:

5'T*C*G*T*CGTTTGAN₁CGN₂*T*T3' (SEQ ID NO: 296)

wherein N₁ is 0-6 nucleotides and optionally is 0-2 nucleotides, wherein N₂ is 0-7 nucleotides, wherein * refers to the presence of a stabilized internucleotide linkage, and 15 wherein the oligonucleotide includes at least 2 phosphodiester internucleotide linkages and optionally the oligonucleotide is 16-24 nucleotides in length.

29. The oligonucleotide of claim 28, wherein the stabilized internucleotide linkage is a phosphorothioate linkage.

30. The oligonucleotide of claim 28, wherein the oligonucleotide has the one of 20 the following structures: 5'T*C*G*T*C*G*TTTTGAN₁C*G*N₂*T*T3' (SEQ ID NO: 296), 5'T*C*G*T*C*G*T*T_GAN₁C*G*N₂*T*T3' (SEQ ID NO: 296), 5'T*C*G*T*C*G*T*T*T*G*A_C_C_G_G_T*T*C*G*T*G*T*T3' (SEQ ID NO: 297), 5'T*C*G*T*C*G*T*T*T*T*G_A_C*G*T*T*T*T*G*T*C*G*T*T3' (SEQ ID NO: 298), 5'T*C*G*T*C*G*T*T_G*A*C*G*T*T*T*T3' (SEQ ID NO: 299), 25 5'T*C*G*T*C*G*T*T_G*A*C*G*T*T3' (SEQ ID NO: 300), or 5'T*C*G*T*C*G*T*T*GA_N₁C*G*N₂*T*T3' (SEQ ID NO: 296).

31. The oligonucleotide of claim 28, wherein the oligonucleotide includes at least one C_G motif with a phosphodiester internucleotide linkage.

32. An oligonucleotide comprising:

30 5' T*C*G*(T*/A*)TN₃CGTTTTN₄CGN₅*T*T3' (SEQ ID NO: 301)

wherein N₃ is 0-4 nucleotides, wherein N₄ is 1-5 nucleotides and optionally is 1-2 nucleotide, wherein N₅ is 0-7 nucleotides, wherein * refers to the presence of a stabilized

internucleotide linkage, and wherein the oligonucleotide includes at least 3 phosphodiester internucleotide linkages and optionally the oligonucleotide is 16-24 nucleotides in length.

33. The oligonucleotide of claim 32, wherein the stabilized internucleotide
5 linkage is a phosphorothioate linkage.

34. The oligonucleotide of claim 32, wherein the oligonucleotide has one of the following structures: 5' T*C*G*(T*/A*)TN₃CGTTTN₄C*G*N₅*T*T 3' (SEQ ID NO: 301), 5' T*C*G*A*T*N₃C*G*TTTN₄C_G_*N₅*T*T 3' (SEQ ID NO: 302), 5'T*C*G*A*T*C*G*T*T*T*T_C_G*T*G*C*G*T*T*T*T3' (SEQ ID NO: 304),
10 5'T*C*G*T*T*T*T*G*A_C_G_T*T*T*T*G*T*C*G*T*T3' (SEQ ID NO: 305) , or 5'T*C*G*T*T*N₃C_G_TTTTN₄CGN₅*T*T 3' (SEQ ID NO: 303).

35. The oligonucleotide of claim 32, wherein the oligonucleotide includes at least one C_G motif with a phosphodiester internucleotide linkage.

36. An oligonucleotide comprising:
15 5'T*C*G*T*C*GNNNCGNCGNNNC*G*N*C*G*T*T3' (SEQ ID NO: 306)
wherein N is any nucleotide, wherein * refers to the presence of a stabilized internucleotide linkage, and wherein the oligonucleotide includes at least 3 phosphodiester internucleotide linkages and optionally 5 phosphodiester internucleotide linkages and wherein the oligonucleotide optionally is 16-24 nucleotides in length.

20 37. The oligonucleotide of claim 36, wherein the stabilized internucleotide linkage is a phosphorothioate linkage.

38. The oligonucleotide of claim 36, wherein the oligonucleotide has one of the following structure: 5'
T*C*G*T*C*G*N*N*N*C_G_N_C_G_N*N*N*C*G*N*C*G*T*T 3' (SEQ ID NO: 307), 5' T*C*G*T*C*G*T*T*A*C_G_N_C_G_T*T*A*C*G*N*C*G*T*T 3' (SEQ ID NO: 308), 5' T*C*G*T*C*G*N*N*N*C_G_T_C_G_N*N*N*C*G*T*C*G*T*T 3' (SEQ ID NO: 309), or 5'
T*C*G*T*C*G*T*T*A*C_G_T_C_G_T*T*A*C*G*T*C*G*T*T 3' (SEQ ID NO: 310).

30 39. An oligonucleotide comprising:
5'T*CGCGN₈CGCGC*GN₉3' (SEQ ID NO: 315)

wherein N₈ is between 4 and 10 nucleotides in length and includes at least 1 C_G motif and optionally at least 2 or 3 CG motifs, wherein N₉ is between 0 and 3 nucleotides in length, wherein * refers to the presence of a stabilized internucleotide linkage, and wherein _ refers to the presence of a phosphodiester internucleotide linkage and wherein 5 the oligonucleotide has a length of 15-40 nucleotides.

40. The oligonucleotide of claim 39, wherein N₈ is PuCGPyPyCG, PuCGPyPyCGCG, or ACGTTCG.
41. The oligonucleotide of claim 39, wherein N₉ includes at least one CG motif.
42. The oligonucleotide of claim 39, wherein N₉ is CCG.
- 10 43. The oligonucleotide of claim 39, wherein the oligonucleotide has the following structure: 5'T*C_G*C_G*A*C_G*T*T*C_G*G*C*G*C_G*C*G*C*C*G3' (SEQ ID NO: 316) or 5'T*C*G*C*G*A*C_G*T*T*C*G*C*G*C_G*C*G*C*G3' (SEQ ID NO: 317).
44. An oligonucleotide comprising:
15 5'T*C_G(N₆C_G N₇)₂₋₃T*C_G*T*T3' (SEQ ID NOs: 311-312)
wherein N₆ and N₇ are independently between 1 and 5 nucleotides in length, and optionally N₆ is one nucleotide, preferably T or A and optionally N₇ is five nucleotides, preferably five pyrimidines or TTTTG wherein * refers to the presence of a stabilized internucleotide linkage, and wherein _ refers to the presence of a phosphodiester
20 internucleotide linkage and wherein the oligonucleotide has a length of 16-40 nucleotides.
45. The oligonucleotide of claim 44, wherein the oligonucleotide has the following structure: 5'
T*C_G*T*C_G*T*T*T*G*A*C_G*T*T*T*T*G*T*C_G*T*T3' (SEQ ID NO:
25 313) or 5' T*C_G*A*C_G*T*T*T*T*G*T*C_G*T*T*T*T*G*T*C_G*T*T3' (SEQ ID NO: 314).
46. An oligonucleotide comprising:
5'T*T*T*GX₁X₂TG X₃X₄T*T*T*T*N₁₀T*T*T*T*T*T*T3' (SEQ ID NO: 18)
wherein N₁₀ is between 4 and 8 nucleotides in length and includes at least 1 C_G
30 motif and optionally includes at least 2 or 3 CG motifs, wherein X₁, X₂, X₃ and, X₄ are independently C or G, wherein * refers to the presence of a stabilized internucleotide

linkage, and wherein _ refers to the presence of a phosphodiester internucleotide linkage and wherein the oligonucleotide has a length of 24-40 nucleotides.

47. The oligonucleotide of claim 46, wherein the oligonucleotide has the following structure:

5 . 5'T*T*G*C_G*T*G*C_G*T*T*T*T*G*A*C_G*T*T*T*T*T*T3' (SEQ ID NO: 319) or 5'T*T*G*G_C*T*G*G_C*T*T*T*T*G*A*C_G*T*T*T*T*T*T3' (SEQ ID NO: 320).

48. An oligonucleotide comprising:

5' T*C*G*C_G*A*C*G*T*T*C_G*G*C*G*C_G*C*G*C*G 3' (SEQ ID NO: 321)

wherein * refers to the presence of a stabilized internucleotide linkage, and wherein _ refers to the presence of a phosphodiester internucleotide linkage and optionally wherein the oligonucleotide has a length of 21-40 nucleotides.

49. An oligonucleotide comprising:

15 an octameric sequence comprising at least one YZ dinucleotide having a phosphodiester or phosphodiester-like internucleotide linkage, and at least 4 T nucleotides, wherein Y is a pyrimidine or modified pyrimidine, wherein Z is a guanosine or modified guanosine, and wherein the oligonucleotide includes at least one stabilized internucleotide linkage.

20 50. The oligonucleotide of claim 49, wherein the octameric sequence includes a TTTT motif.

51. The oligonucleotide of claim 49, wherein the octameric sequence includes two YZ dinucleotides.

25 52. The oligonucleotide of claim 51, wherein both YZ dinucleotides have a phosphodiester or phosphodiester-like internucleotide linkage.

53. The oligonucleotide of claim 49, wherein Y is an unmethylated C.

54. The oligonucleotide of claim 49, wherein Z is a guanosine.

55. The oligonucleotide of claim 49, wherein the octameric sequence is selected from the group consisting of T*C-G*T*C-G*T*T, C-G*T*C-G*T*T*T, G*T*C-G*T*T*T*T, T*C-G*T*T*T*T*G, C-G*T*T*T*T*G*A, T*T*T*T*G*A*C-G, T*T*T*T*G*A*C-G*T, T*T*G*A*C-G*T*T, T*G*A*C-G*T*T*T, G*A*C-G*T*T*T*T, A*C-G*T*T*T*T*G, C-G*T*T*T*T*G*T, T*T*T*T*G*T*C-G,

T*T*T*G*T*C-G*T, G*T*T*T*T*G*T*C, and T*T*G*T*C-G*T*T, wherein * refers to the presence of a stabilized internucleotide linkage, and wherein _ refers to the presence of a phosphodiester internucleotide linkage.

5 56. The oligonucleotide of claim 49, wherein the oligonucleotide has a length of
8-40 nucleotides.

57. The oligonucleotide of claim 49, wherein the phosphodiester-like linkage is
boranophosphonate or diastereomerically pure Rp phosphorothioate.

10 58. The oligonucleotide of claim 49, wherein the stabilized internucleotide
linkages are selected from the group consisting of: phosphorothioate,
phosphorodithioate, methylphosphonate, methylphosphorothioate, and any combination
thereof.

15 59. The oligonucleotide of claim 49, wherein Y is cytosine or a modified
cytosine bases selected from the group consisting of 5-methyl cytosine, 5-methyl-
isocytosine, 5-hydroxy-cytosine, 5-halogeno cytosine, uracil, N4-ethyl-cytosine, 5-
fluoro-uracil, and hydrogen.

20 60. The oligonucleotide of claim 49, wherein Z is guanine or a modified guanine
base selected from the group consisting of 7-deazaguanine, 7-deaza-7-substituted
guanine (such as 7-deaza-7-(C2-C6)alkynylguanine), 7-deaza-8-substituted guanine,
hypoxanthine, 2,6-diaminopurine, 2-aminopurine, purine, 8-substituted guanine such as
8-hydroxyguanine, and 6-thioguanine, 2-aminopurine, and hydrogen

25 61. The oligonucleotide of claim 49, wherein the oligonucleotide has a 3'-3'
linkage with one or two accessible 5' ends.

62. The oligonucleotide of claim 49, wherein the oligonucleotide has two
accessible 5' ends, each of which are 5'TCG.

25 63. The oligonucleotide of claim 49, wherein the oligonucleotide a sequence
selected from the group consisting of CGTCGTTTGACGTTTGTCTT (SEQ ID
NO: 333), GTCGTTTGACGTTTGTCTT (SEQ ID NO: 334),
TCGTTTGACGTTTGTCTT (SEQ ID NO: 335), CGTTTGACGTTTGTCTT
(SEQ ID NO: 336), GTTTGACGTTTGTCTT (SEQ ID NO: 337),
30 TTTTGACGTTTGTCTT (SEQ ID NO: 338), TTTGACGTTTGTCTT (SEQ ID
NO: 339), TTGACGTTTGTCTT (SEQ ID NO: 340), TGACGTTTGTCTT (SEQ
ID NO: 341), GACGTTTGTCTT (SEQ ID NO: 342), ACGTTTGTCTT (SEQ ID

NO: 343), GTTTGTCGTT (SEQ ID NO: 344), GTTTGTCGTT (SEQ ID NO: 345), TTTGTCGTT (SEQ ID NO: 346), TTTGTCGTT, and TTGTCGTT.

64. The oligonucleotide of claim 49, wherein the oligonucleotide a sequence selected from the group consisting of TCGTCGTTTGACGTTTGTGCGT (SEQ ID NO: 347), TCGTCGTTTGACGTTTGTGCG (SEQ ID NO: 348), TCGTCGTTTGACGTTTGTGTC (SEQ ID NO: 349), TCGTCGTTTGACGTTTGTG (SEQ ID NO: 350), TCGTCGTTTGACGTTTGTG (SEQ ID NO: 351), TCGTCGTTTGACGTTT (SEQ ID NO: 352), TCGTCGTTTGACGTTT (SEQ ID NO: 353), TCGTCGTTTGACGTT (SEQ ID NO: 354), TCGTCGTTTGACGT (SEQ ID NO: 355), TCGTCGTTTGACG (SEQ ID NO: 356), TCGTCGTTTGAC (SEQ ID NO: 357), TCGTCGTTTGGA (SEQ ID NO: 358), TCGTCGTTTG (SEQ ID NO: 359), TCGTCGTTT (SEQ ID NO: 360), TCGTCGTT, and TCGTCGTT.

65. The oligonucleotide of claim 49, wherein the oligonucleotide a sequence selected from the group consisting of CGTCGTTTGACGTTTGTGCGT (SEQ ID NO: 361), GTCGTTTGACGTTTGTGCG (SEQ ID NO: 362), TCGTTTGACGTTTGTGTC (SEQ ID NO 363), CGTTTGACGTTTGT (SEQ ID NO: 364), GTTTGACGTTT (SEQ ID NO: 365), TTTTGACGTTT (SEQ ID NO: 366), TTTGACGTTT (SEQ ID NO: 367), and TTGACGTT.

66. An oligonucleotide comprising:
20 5' TCGTCGTTTGACGTTTGTGCGT 3' (SEQ ID NO: 368)
wherein at least one CG dinucleotide has a phosphodiester or phosphodiester-like internucleotide linkage, and the oligonucleotide includes at least one stabilized internucleotide linkage.

67. An oligonucleotide comprising:
25 5'GNC 3', wherein N is a nucleic aid sequence of 4-10 nucleotides in length and is at least 50% T and does not include a CG dinucleotide, and the oligonucleotide includes at least one stabilized internucleotide linkage.

68. The oligonucleotide of claim 67, wherein N includes a TTTT motif.
69. The oligonucleotide of claim 68, wherein the oligonucleotide is selected
30 from the group consisting of G*T*T*T*T*G*T*C and G*T*T*T*T*G*A*C, wherein * refers to the presence of a stabilized internucleotide linkage.

70. A method for modulating an immune response, comprising administering to a subject an oligonucleotide of any one of claims 1-69, in an effective amount to modulate an immune response.

5 71. The method of claim 70, wherein the oligonucleotide is delivered to the subject to treat asthma in the subject.

72. The method of claim 70, wherein the oligonucleotide is delivered to the subject to treat allergy in the subject.

73. The method of claim 70, wherein the oligonucleotide is delivered to the subject to treat cancer in the subject.

10 74. The method of claim 70 wherein the oligonucleotide is delivered to the subject to treat an infectious disease in the subject.

75. The method of claim 70, wherein the oligonucleotide is delivered to the subject to treat autoimmune disease in the subject.

15 76. The method of claim 70, wherein the oligonucleotide is delivered to the subject to treat airway remodeling in the subject.

77. The method of claim 70, further comprising administering with or without an antigen to the subject.

78. The method of claim 70, further comprising administering a therapeutic protocol to the subject.

20 79. The method of claim 78, wherein the therapeutic protocol is surgery.

80. The method of claim 78, wherein the therapeutic protocol is radiation.

81. The method of claim 78, wherein the therapeutic protocol is a medicament.

82. The method of claim 70, wherein the oligonucleotide is formulated.

25 83. The method of claim 82, wherein the oligonucleotide is associated with a targeting molecule.

84. The method of claim 70, wherein the oligonucleotide is delivered by a route selected from the group consisting of oral, nasal, sublingual, intravenous, subcutaneous, mucosal, respiratory, direct injection, and dermally.

30 85. The method of claim 70, wherein the oligonucleotide is delivered to the subject in an effective amount to induce cytokine expression.

86. The method of claim 85, wherein the cytokine is selected from the group consisting of IL-6, TNF α , IFN α , IFN γ and IP-10.

87. The method of claim 70, wherein the oligonucleotide is delivered to the subject in an effective amount to shift the immune response to a Th1 biased response from a Th2 biased response.

88. A method for treating airway remodeling, comprising:
5 administering to a subject an oligonucleotide comprising a CG dinucleotide, in an effective amount to treat airway remodeling in the subject.

89. The method of claim 88, wherein the subject has asthma.

90. The method of claim 88, wherein the subject has chronic obstructive pulmonary disease.

10 91. The method of claim 88, wherein the subject is a smoker.
92. The method of claim 88, wherein the subject is free of symptoms of asthma.
93. The method of claim 88, wherein the oligonucleotide is an oligonucleotide of any one of claims 1-66.
94. A method for stimulating an immune response, comprising
15 administering to a subject an oligonucleotide of at least 5 nucleotides in length in an effective amount to stimulate an immune response, wherein the oligonucleotide includes at least one immunostimulatory dinucleotide motif wherein the internucleotide linkage between the nucleotides of the dinucleotide has R chirality and wherein at least 70% of the other internucleotide linkages of the oligonucleotide have S chirality.